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Hypoglycemia in a dog due to an insulinoma was first reported in the literature in 1927. Although there have been many reported cases since that time, it is still considered to be a fairly rare condition by most authors. Its frequency, however, is probably much greater than the literature would lead one to believe, as the vast majority of cases go unreported or unrecognized. The Iowa State University Teaching Hospital alone diagnoses three or four cases each year, which is a substantial number in light of the fact that functional beta cell tumors have been reported in only 45 dogs.[7]

The hallmark of this syndrome is a "mature onset" hypoglycemia, which results from the excessive production and inappropriate secretion of insulin from the neoplastic beta cells.

The maintenance of blood glucose concentration (normally 70 to 110 mg/dl in the dog) depends upon several factors: (1) adequate intake and absorption of nutrients, (2) normal liver function, and (3) the synthesis and release, in appropriate amounts, of insulin, cortisol, glucagon, epinephrine, and growth hormone.[11] Thus a hypoglycemic condition or episode has several possible etiologies which must be considered; it is but the sign of a more specific defect somewhere in the complex blood glucose homeostatic system.

As a diagnostic aid, the causes of hypoglycemia may be divided into two categories. One group includes those problems related to intestinal absorption and/or hepatic production of glucose; i.e., where an inadequate amount of glucose is being provided to the blood. Chronic starvation or malabsorption, glycogen storage diseases in the young ("juvenile onset" hypoglycemia), and acute or chronic liver failure are in this group. (It should be noted, however, that although hepatic disease can be responsible for a hypoglycemia, the function to maintain blood glucose concentration is usually not lost unless the entire liver is involved,[11] such that other signs would likely appear before and predominate over the hypoglycemic state.)

The second group involves those problems which lead to an increased rate of removal of glucose from the blood; i.e., increased peripheral utilization of glucose. (In man, renal tubular glycosuria must also be considered, but this condition, although it occurs in the dog, has not been shown to be associated with hypoglycemia.[7]) It is this effect which leads to a hypoglycemia in the case of insulinomas, insulin overdose, or posioning with sulfonylurea compounds, such as tolbutymide (which apparently act by stimulating the release of insulin from the beta cells). In these cases, the peripheral glucose utilization is primarily in the form of glycogen deposition and lipogenesis. The functional hypoglycemia seen in hunting dogs may also be included in this group, as the hypoglycemic episodes are precipitated by strenuous muscular exercise, hence an increased peripheral glucose utilization, but in this case via glycolysis (increased energy demands). However, there are some who feel that this malady has as its underlying etiology some type of glycogen storage deficiency.[7]

The presenting signs associated with a hypoglycemia, regardless of etiology, are those of a neurologic dysfunction—a reflection of the great dependency of the central nervous system upon blood glucose concentration. Two factors are responsible for this dependency: (1) the unavailability of glycogen stores and (2) the fact that neurons rely upon passive diffusion for their glucose supply; i.e., insulin is not involved. The severity of the signs seen is said to be more

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dependent upon the rate at which blood glucose concentration declines than upon the actual degree of hypoglycemia,[7] indicating that there is some ability for the brain to adapt to low blood glucose levels. This helps to explain the variability and progression of symptoms reported by the owners of insulinoma dogs. It also explains why insulinoma dogs, when presented for clinical examination, may appear normal in every respect and yet frequently have blood glucose concentrations which are well below the normal range.

The functional disturbances characteristically reported in insulinoma cases are episodic in nature, occurring initially at widely spaced intervals which become more frequent and severe as the condition progresses, until grand mal-type seizures may be an almost daily event.[1] Early signs frequently reported include weakness, particularly of the hindquarters, fatigue after exercise, trembling, generalized muscular twitching, changeable temperament, incoordination and ataxia. In more advanced cases, confusion and disorientation or apparent blindness, retching, vomiting, and tono-clonic consulvions, often lasting 10 to 15 minutes or more are commonly seen. However, in some cases there may be no history of any type of dysfunction prior to the onset of seizure activity, and the dog will be completely normal between episodes, while in other cases there may be no history of seizures at all.[1,2,5,6,7,9]

If recurrent seizures are included in the history, and they usually are, several differential diagnoses must be included. These include idiopathic epilepsy, brain tumor, encephalitis, lead posioning, hypoparathyroidism, and cardiovascular or respiratory diseases which could lead to cerebral ischemia (which can cause seizures) as well as hypoglycemia.[6,7] Causes of seizures outside the nervous system should be eliminated before causes inside the nervous system are sought.[6] The physical exam should reveal evidence of cardiovascular or respiratory disease, such as arrhythmias, murmurs, ascites, or dyspnea. The history should indicate whether or not access to lead might be a possibility. Blood or urine lead level determinations are necessary for confirmation. Hypoparathyroidism, an extremely rare disease in the dog,[7] can be ruled out based on the analysis of blood calcium and phosphorus levels.

Unfortunately, hypoglycemia in general, and insulinoma in particular, cannot be as easily ruled out, nor ruled in, as the cause for recurrent seizures simply on the basis of a single blood glucose determination. A dog with an actively secreting beta cell tumor, if in an apprehensive and excited state when brought into the exam room, may have enough of an epinephrine response to elevate the blood glucose level to well into the normal range. Moreover, a dog with idiopathic epilepsy or a brain tumor may be found to be hypoglycemic, as this is not an uncommon incidental finding during routine screening of mature dogs.[7] This is not to say that a fasting blood glucose determination is not a valuable diagnostic aid as long as it is interpreted as suggestive evidence rather than proof. Indeed, a fasting blood glucose concentration of less than 40 mg/dl is adequate for a presumptive diagnosis of insulinoma in an adult dog suffering from recurrent seizures. In some cases a 48 hour fast may be necessary to see glucose levels fall that low, but usually a 12 to 24 hour fast is adequate. It is always a good idea to repeat the test three times before deciding whether or not more provocative tests are indicated. The best time to draw blood for the test is early in the morning, when the dog is quiet.

The history can also provide some important differentiating clues, which can be especially helpful in determining what further course be followed for the diagnosis of cases where the results of the fasting glucose tests are questionable. It is important to ascertain the duration and progression of signs, as insulinoma dogs frequently have long histories of neurologic disturbances. Also, there is frequently a common pattern to the occurrence of seizures in that they are often associated with fasting periods (such as early in the morning, before feeding), exercise, or in many cases closely following a meal, as carbohydrates and some amino acids act as a stimulus for insulin release. The age of the animal is also important, as insulinomas occur most frequently in older dogs, the average age being about nine years.[7]

The best tests available today for confirming a diagnosis of insulinoma are the glucagon tolerance test, the insulin radioimmunoassay, and the high-dose in-

travenous glucose tolerance test (H-IVGTT). Very low glucose concentrations (less than 40 mg/dl) in three consecutive fasting blood glucose determinations can also be considered nearly pathognomonic. Other tests used in the past have been discounted due to dangers involved with their use or their inability to positively differentiate insulinomas from other causes of hypoglycemia.[2,7,9] Although the H-IVGTT is useful for evaluating the ability of an animal to shift glucose out of the plasma space, the results obtained with this test in cases of insulinomas are not as consistent as those obtained with the glucagon tolerance test. This is because the H-IVGTT depends upon an acute outpouring of insulin from the neoplastic beta cells in response to the hyperglycemia created by rapid intravenous injection of glucose (1 Gm/Kg of body weight). This does not always occur.[12] Glucagon, on the other hand, provokes the release of insulin both directly (within three minutes after intravenous injection) and indirectly via its rapid glycogenolytic effect (15 to 30 minutes after injection).[7]

The glucagon tolerance test is preferably run after a 12 hour fast. An IV dose of 0.03 mg glucagon/kg of body weight is administered after blood is drawn for a preinjection blood glucose evaluation. Blood glucose concentration is then determined for samples taken at 1, 3, 5, 15, 30, 45, 60, 90, 120 and 180 minutes. An exaggerated insulin response is expected if the patient has a functional beta cell tumor. Peak blood glucose concentrations will usually not exceed 140 mg/dl, whereas normal dogs will peak in the range of 180 to 200 mg/dl. More importantly, the neoplastic outpouring of insulin causes a much more rapid fall in blood glucose levels, such that a profound hypoglycemia (less than 50 mg/dl) occurs 45 to 90 minutes after administration.[2,4,7] Seizures may accompany the hypoglycemia, so glucose should be available for intravenous administration. In normal dogs, the blood glucose concentration will decline more slowly, remaining elevated for more than two hours.[2]

The newest test for the positive diagnosis of insulinoma is the insulin radioimmunoassay (insulin-RIA), in which plasma insulin levels are determined directly. The normal fasting level is about 20 uU/ml; insulinoma dogs usually have values of over 50 uU/ml.[2] In fasting hypoglycemia due to other causes, such as malabsorption, plasma insulin levels are usually normal to subnormal.[7] The insulin to glucose ratio is thus the most important criterion of the test, as it is a statement of cause and effect. Immunoreactive insulin concentrations determined for samples drawn during a glucagon tolerance test will give dramatic evidence, which is clearly diagnostic, of this cause and effect relationship.[7]

In man, up to 90% of insulinomas are benign. In the dog, the majority are malignant.[1] These carcinomas are usually large, multilobular, and invade extensively into the adjacent parenchyma and lymphatics. The establishment of metastases in extrapancreatic sites, including lymph nodes, liver, mesentery, and omentum, occurs early in the disease, frequently before the diagnosis can be made. (The early phases of the disease are masked by an increased secretion of the anti-insulin hormones—glucocorticoids, glucagon, epinephrine and STH.[10]) As a result, eliminating the source of the excess insulin via surgical extirpation of the pancreatic lesion, which would obviously be the treatment of choice, is not often possible.

In cases in which the hyperinsulinism is due to a single functional adenoma, surgical removal of the portion of the pancreas containing the neoplastic tissue can result in a dramatic amelioration of the hypoglycemia and its attendant signs, unless there have been irreversible changes in the CNS.[12] In contrast to carcinomas, adenomas are sharply delineated and encapsulated, making successful surgical excision possible.[1] They can mobilize, however, so it is wise to check the entire pancreas to detect other tumors. Although the neoplasm is usually of significant size to be palpable and observable, in some cases the tumor cannot be identified during the exploratory laparotomy, and in these cases, a total pancreatectomy would be required. Although this is not a difficult procedure, the owner should be forewarned of the necessity for special diets and insulin and pancreatic enzyme supplementation, which will be required for the remainder of the animal's life.[3] Other important considerations are that postsurgical complications, such as pancreatitis, are common, and that the older age of the dog may make the patient a poor surgical risk.

During and immediately after the surgical procedure, it is important to maintain a continuous IV drip of 5 or 10 percent dextrose solution, as well as continuously monitoring the blood glucose level, since palpation of the tumor may result in considerable insulin release.[3,12] Since postsurgical idiopathic hyperthermia has been observed, corticosteroids prior to surgery are recommended as prophylaxis.[7,12]

Postsurgically, the partial pancreatectomy patient may become *hyper*glycemic for a few hours or days. Two possible reasons are (1) an excess of anti-insulin hormones and/or (2) depression of the secretory activity of the non-neoplastic beta cells in the remainder of the pancreas due to long term suppression by the elevated insulin levels.[1] Postsurgical care is directed primarily toward prevention of pancreatitis and consists of food restriction, the administration of corticosteroids and parasympatholytic agents, and parenteral fluid therapy.[1,12] Serum amylase activity is useful as an indicator of the severity of postsurgical pancreatitis, but some elevation can be expected to occur for 7 to 10 days.[1]

Lymph node enlargement and yellow-white foci in the liver are suggestive of metastasis of islet cell carcinomas. Although the prognosis in such a case is poor, a total pancreatectomy may be of some benefit in prolonging the life of the patient, as the carcinomas tend to be slow growing.[1] Dietary management is very important, as glucose and some amino acids stimulate insulin secretion, whereas lipids do not. Therefore the diet should include fats as the main source of energy, well-balanced protein just adequate to meet maintenance requirements, and minimal amounts of carbohydrates. Diazoxide and hydrochlorothiazide are hyperglycemic agents which may be useful for symptomatic treatment in metastasized cases or in cases where surgery is not advisable or desired. Frequent feedings are also helpful in controlling hypoglycemia.

Conclusion

Although canine insulinoma is considered to be a fairly rare condition, its occurrence is frequent enough that it should be included in the differential diagnosis anytime a dog is presented with a history of recurrent seizures. Also, it is important that an adequate battery of tests be used before the condition is ruled out. This should include at least three fasting blood glucose determinations, followed by a glucagon tolerance test or high-dose intravenous glucose tolerance test, preferably in combination with an insulin radioimmunoassay for positive diagnosis in questionable cases.

Early diagnosis is of paramount importance if surgical excision of the tumor is to be curative; in most cases, due to the high incidence of malignancy and early metastasis, it is only palliative. Yet despite the poor long-term prognosis, proper home care, including dietary management and the use of hyperglycemic drugs, coupled with surgery when possible, can extend life for a reasonable period of time. Before any course of therapy is instituted, the owner should be educated as to the possible complications of surgery, the high incidence of malignancy, and the trouble and expense involved with maintenance of the patient following pancreatectomy.

References

1. Capen CC, Belshaw BE, Martin SL: Hyperinsulinism. *Textbook of Veterinary Internal Medicine,* Vol. 2, W. B. Saunders Co., Phila. 1975 pp. 1438-1447.
2. Chastain CB: Small Animal Clinical Endocrinology lecture notes, ISU College of Vet. Med., 1977, pp. 112-117.
3. Dingwall JS: The Pancreas. *Current Techniques in Small Animal Surgery,* Lea and Febiger, Phila. 1975 pp. 151-155.
4. Duncan JR, Prasse KW: *Veterinary Laboratory Medicine,* ISU Press, 1977 pp. 133-138.
5. Hoerlein BF: Diseases with clinical signs related to the brain. *Canine Neurology, Diagnosis and Treatment,* W. B. Saunders Co., Phila. 1971 pp. 475-477.
6. Holiday T: Clinical Neurology lecture notes, 1979, pp. 236-241.
7. Johnson RK, Atkins CE: Hypoglycemia in the dog. *Kirks Current Veterinary Therapy VI,* W. B. Saunders Co., Phila. 1977 pp. 1010-1016.
8. McDonald LE: *Veterinary Endocrinology and Reproduction,* Lea and Febiger, Phila. 1975 pp. 121-128.
9. Njoka CO, Strafuss AC, Dennis AM: Canine islet cell neoplasia, a review, *JAAHA,* 1972, Vol. 8 pp. 284-288.
10. Siddons EB, Carithers RW: Canine Insulinoma, *ISU Veterinarian,* Vol. 38 No. 2, 1976, pp. 60-65.
11. Strombeck DR, et. al.: Hypoglycemia and hypoinsulinemia associated with hepatoma in a dog, *JAVMA,* Oct. 15, 1976, Vol. 169 pp. 811-812.
12. Wilson JW, Hulse DA: Surgical correction of islet cell adenocarcinoma in a dog, *JAVMA,* March 15, 1974, Vol. 164 pp. 603-606.